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## ROLE OF TISSUE ADHESIVE IN OTORHINOLARYNGOLOGY

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### Abstract:

This paper summarises the effectiveness of tissue adhesives in otorhinolaryngology. Although the adhesion system cannot and should not replace surgical suture, it provides valuable assistance in tissue synthesis and in local haemostasis, particularly in cases where conventional suture methods are especially difficult to apply. In addition to good adhesion, an elastic consistency, and good tissue compatibility, the adhesive is completely absorbed. The system has been used successfully in myringoplasty, laryngectomy during pharyngeal closure, repair of CSF leak, laryngocele, and ossiculoplasty.

### Introduction:

The idea to use adhesives for wound closure or to stabilize and fix tissues can be traced back to many centuries. After the use of different adhesives and glutinous substances (pitch, bee wax, natural rubber) for wound cover with more or less good results, the development of fibrin glues (1940) and the later cyanoacrylates (1960) offered new ways in tissue adhesion.

The gold standard of wound closure, the suture, becomes less possible because of Continuous miniaturisation and the development of minimally invasive surgery methods, particularly in mucosal areas. But a sufficient wound closure, a secured fixation of skin grafts, transplants and implants can be of vital importance for the success of a surgical therapy. In these areas, tissue adhesives virtually present themselves as method of choice. Gluing ensures a constant laminar force spreading. Unevenness of the material can be

compensated by the adhesive. Additionally to mechanical and chemical basics of adhesion, the characteristics of a living system must be considered for medical application.

The requirements of medical tissue adhesive:

**Biocompatibility:**

- Biodegradation and resorbability in a defined period
- no local or systemic toxicity, carcinogenicity or teratogenicity of the adhesives or its degradation products
- marginal heat development during hardening.

**Compound strength:**

- high bond strength in wet environment with immediate functional stress
- adequate elasticity

**Application:**

- easy preparation
- adequate flow characteristics and curing times
- application systems for different areas of application
- miniaturisation (microscopic and endoscopic surgical methods)

**Others:**

- Sterilisability
- Stable to storage

**Materials and methods:**

A study was conducted in Stanley medical college and hospital from 2009 to 2011. Tissue glue was used in various surgeries like myringoplasty, total laryngectomy (pharyngeal closure), repair of CSF leak and laryngocele and the effectiveness was evaluated. We used Biologic tissue adhesive, 'Tisseel' a two component fibrin sealant.

### **Tisseel kit contains:**

Tisseel, lyophilized, stream treated sealer protein concentrate, human 1 ml of Tisseel solution contains

Clottable protein                      75- 115 mg

Thereof fibrinogen                    70-110 mg

Plasma fibrinogen (CIG)            2-9 mg

Factor XIII                              10-15 IU

Plasminogen                            40-120 ug

Aprotinin solution bovine, 3000 KIU/ml

Thrombin 4 lyophilized, human 1 ml of thrombin solution contains

Thrombin 4 IU

Thrombin 500 lyophilized, human 1 ml of thrombin solution contains

Thrombin 500 IU

Calcium chloride solution 40 mmol/l

Kits for reconstruction and application.





Image showing TISSEEL KIT



Image showing syringe used for tissue glue application

Mechanism of adhesion: <sup>1</sup>

The components thrombin and fibrinogen cause, analogue to the last phase of blood coagulation, the formation of cross-linked fibrin. Here, the concentration of fibrinogen is 15 to 25 times higher than in circulating plasma. Therefore, fibrin is formed much faster. The other key factor is factor XIII, which causes an indissoluble fibrin matrix. Besides, most fibrin glues contain anti-fibrinolytic substances (tranexamic acid, aprotinin), which are responsible for stabilisation of the adhesion by inhibition of fibrinolysis. <sup>1,2</sup> It is elaborated in detail in discussion.

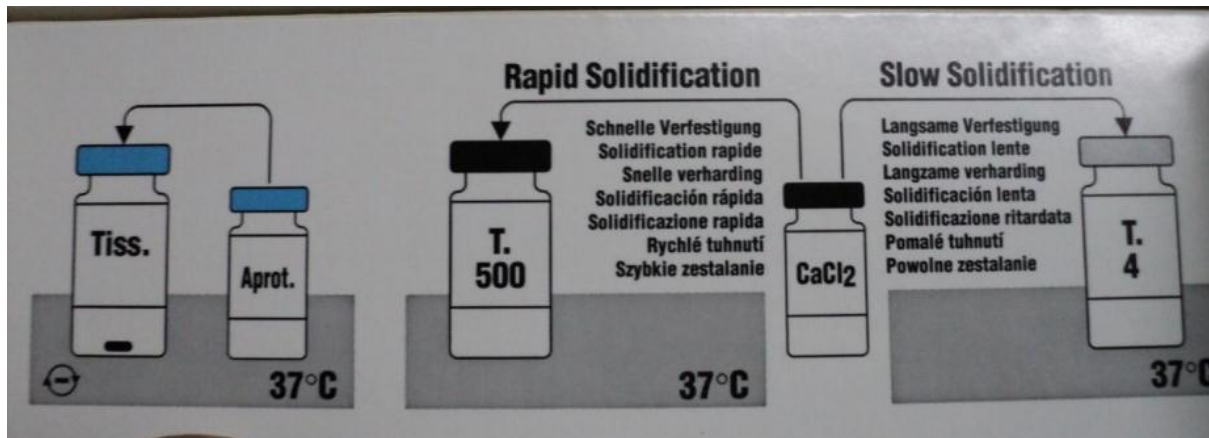


Image describing reconstruction process

### Reconstruction and application:

Use Tisseel and Thrombin solution within 4 hrs. after reconstitution.

### Caution:

Use separate syringes and needles for reconstitution of Tisseel and thrombin.

Use again separate syringes and needles for their application.

Do not inject by the intravenous route.



## **Application:**

### **Study 1:**

This fibrin glue was used in 10 cases of myringoplasty. 7 Myringoplasty was done as classical underlay technique. Graft was placed lateral to the handle of malleus and fibrin glue was applied at the margins of the tympanomeatal flap after it was repositioned. And those cases were followed up for a period of 6 months (once in every month) and the cases were evaluated by otoendoscopy and pure tone audiometry.

Otoendoscopy was done and the following features were assessed:

Graft taken up or not.

Graft medialisation.

Graft lateralisation.

**Results:** Graft was taken up in 9 out of 10 cases. There is neither lateralisation nor medialisation of the graft. Pure tone audiometry was showed there was improvement in air bone gap.

### **Study 2:**

Fibrin glue was applied in a case of total laryngectomy after closure of the pharynx.<sup>8</sup> Especially here it was applied not to replace the surgical suture but to provide valuable assistance to the tissue synthesis and for local haemostasis.



Figure showing glue being applied in a patient with total laryngectomy

Sutures were first removed alternatively, and completely removed at 18th post-operative day. There was no pharyngo cutaneous fistula. Case was followed up once in a month for 3 months. There is neither fistula formation nor inflammatory reaction.

### **Study 3:**

Fibrin glue was also used in cleft palate repair. It was applied after closure of the muscle layer and mucosal layer. During post-operative follow up the wound was found to be healthy and there is no palatal fistula.



Application of tissue glue in cleft palate repair

### **Study 4:**

Tissue glue is used in external laryngocoe surgery. Laryngocoele was resected from its attachments near the thyrohyoid membrane and tissue glue is applied to seal the defect in the thyrohyoid membrane. No recurrence was noted in the one year follow up period.

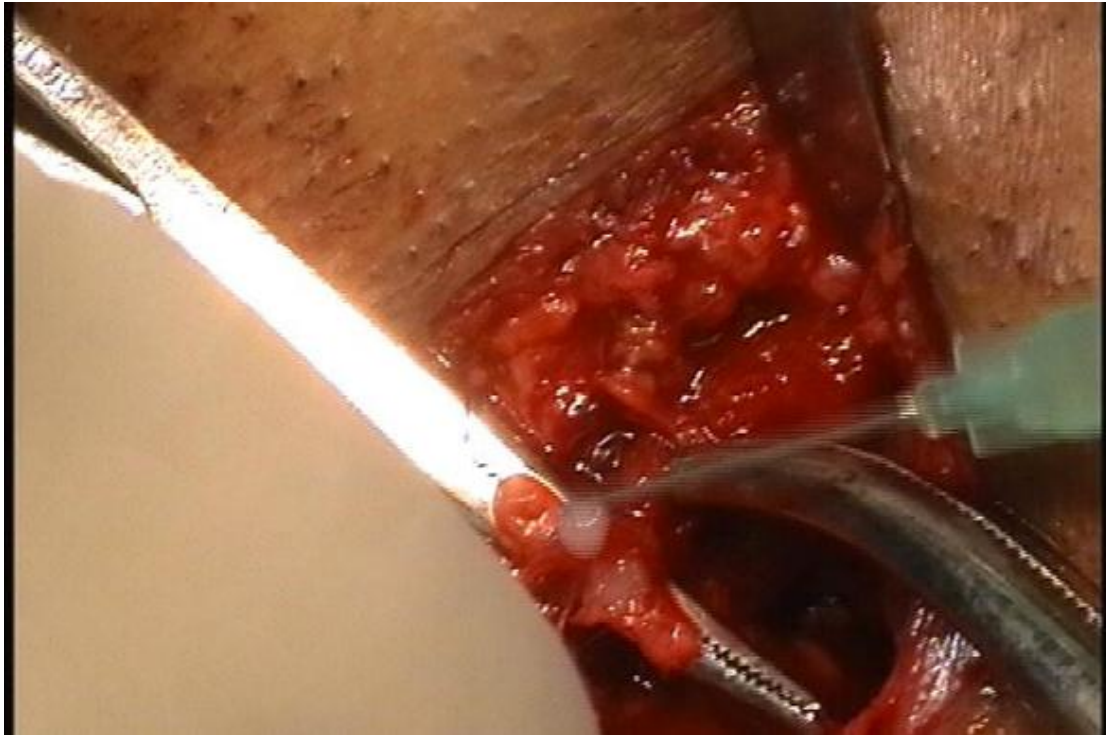


Image showing tissue glue being applied after laryngocele excision

#### **Study 5:**

CSF leak repaired through bicoronal approach. Bicoronal approach was used to expose anterior table of the frontal sinus. A window was created in the anterior table of the frontal sinus using the fissure burr. The interior of the frontal sinus was visualised and the leak site was identified over the posterior table of the left frontal sinus which was sealed using tissue glue and abdominal fat. No recurrence was noted in the 6 months follow up period.



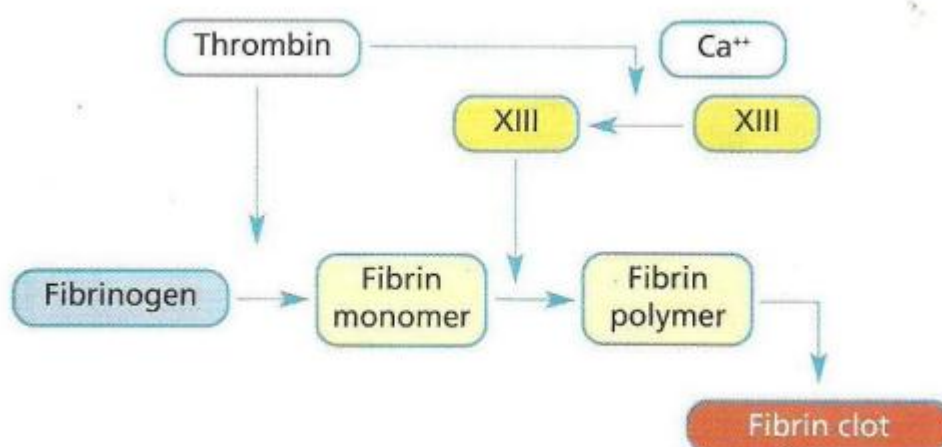


Tissue glue used in CSF leak repair

**Discussion:**

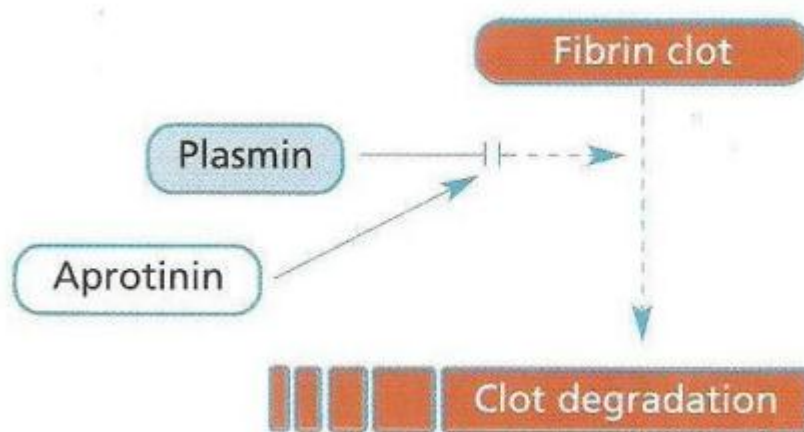
Fibrin glues are used since 1940. These are the most commonly used tissue adhesives.

Mechanism of adhesion:



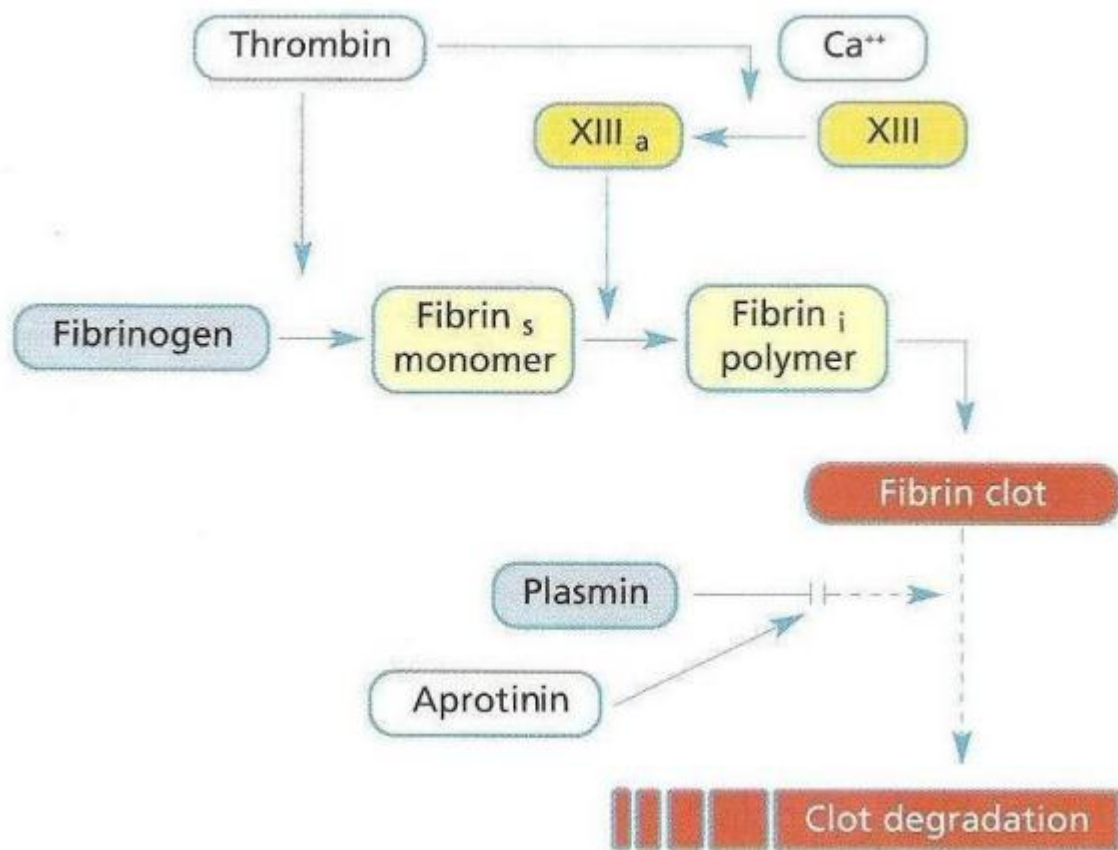
### The principle of biological sealing:

In the last step of the coagulation cascade fibrinogen is transformed to fibrin monomers which aggregate and form a gel. Concomitantly, thrombin transforms factor XIII to factor XIIIa in the presence of calcium ions. Factor XIIIa crosslinks the aggregated fibrin monomers to a high molecular weight polymer. The resulting fibrin clot seals off surrounding tissue and provides early haemostasis.



### FIBRIN GLUE REPRODUCES THE LAST STEP OF THE COAGULATION CASCADE:

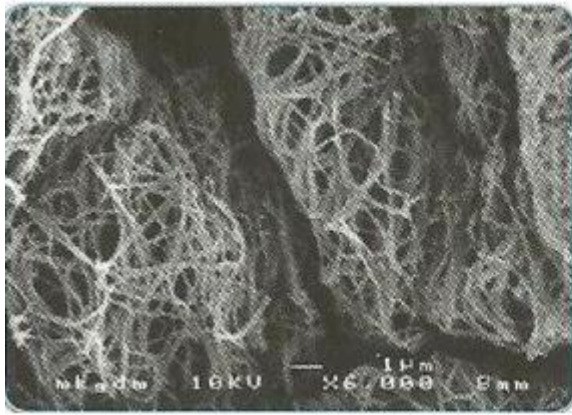
In natural conditions the fibrin clot is degraded after 1-2 days in most tissues. Fibrin glue contains aprotinin- the most effective exogenous antifibrinolytic (clot stabilizer) known to inhibit not only plasminogen activation and plasmin binding but most proteases involved in clot degradation. It is added to fibrin glue to prolong its stability in vivo up to 9-10 days. Factor XIII crosslinks fibrin monomers and also fibrin and fibronectin with the collagen of the tissue to which the sealant was applied.



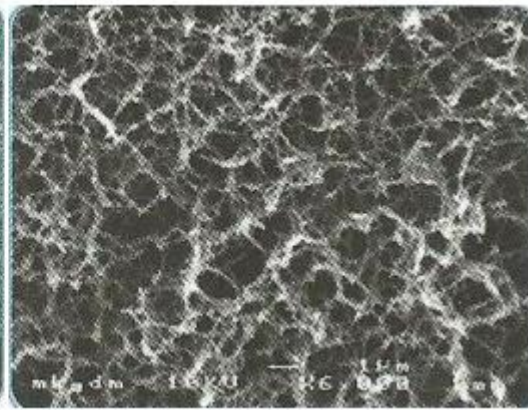
The fibrin glue clot contains 30 times the fibrinogen concentration, provides high elasticity and 4-5 times greater tensile strength than a normal blood clot.

Fibrinogen concentration is directly proportional to:

- Elasticity of the fibrin clot
- Increased tensile strength
- Increased adhesive strength



Blood clot



Fibrin glue clot

All components of a fibrin glue matrix are involved in the process of wound healing.

Thrombin	Activation of wound healing related receptors.
Fibrinogen	Stimulation of angiogenesis and promoting cell adhesion and migration
FactorXIII	.crosslinking fibronectin and other molecules with fibrin and collagen
Fibronectin	Providing binding sites for cells involved in wound healing

#### **Advantages of these biologic tissue adhesives:**

- Good adhesion in wet environment
- Minimal tissue irritation
- Good sealing without heat development
- Curing time is better

#### **Disadvantages:**

- There is a minimal risk of transmission of prions by aprotinin with bovine origin 1,3
- Cannot be used in arterial bleeding (even heavy venous bleeding is contraindicated)
- Cannot be used in persons with allergic heparin induced thrombocytopenia, and who are intolerance to bovine products.

## **SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE:**

1. For epilesional use only. Soft tissue injection carries the risk of an anaphylactoid reaction and /or local tissue damage
2. Life threatening anaphylactiod reactions and/or thromboembolic complications may occur if the preparation is unintentionally applied intravascularly.
3. It should be applied as a thin layer. Excessive clot thickness may negatively interfere with the products efficacy and wound healing process.
4. Fibrin glue contains bovine protein (aprotinin). Even in the strict local application, there is a risk of anaphylactoid reaction, linked to the presence of bovine aprotinin. The risk seems higher in case of previous exposure even it was well tolerated.
5. Therefore any use of aprotinin containing products should be recorded in the patient's records.
6. In case of shock, standard medical treatment for shock should be implemented.
7. Signs of hypersensivity reactions include hives, generalised urticaria, and tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur the administration has to be discontinued immediately.
8. Thrombin and factor XIII are made from human plasma. Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations.
9. Despite this, the possibility of transmitting infective agents cannot be totally excluded. this also applies to unknown or emerging viruses or other pathogens. The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV. The measures taken may be of limited value against small non-enveloped viruses such as parvovirus B 19 AND HAV.
10. The hypersensitive and anaphylactoid reactions especially may be seen, if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to aprotinin or any other constituents of the products. Even if the second treatment with fibrin glue was well tolerated, a subsequent administration may result in severe anaphylactoid reactions.



Other than biologic tissue adhesives some other adhesives also in use. They are

- Synthetic adhesives (cyanoacrylates)
- Gelatine resorcinol formaldehyde/glutaraldehyde glues
- Albumin glutaraldehyde glue

### **Synthetic adhesives:**

This has been described for the first time in 1959. <sup>1,4</sup>.

But the first short chain cyanoacrylates turned out to be histotoxic and caused distinct foreign body reactions. The long chain cyanoacrylates of the second generation are more biocompatible. <sup>5,6</sup> With raising chain length ,toxicity and adhesion strength decrease, elasticity and polymerisation time increase.

First generation:

- Methyl cyanoacrylate

Second generation:

- Ethyl 2 cyanoacrylate
- n butyl cyanoacrylate
- 2 octyl cyanoacrylate
- Isobutyl cyanoacrylate
- N butyl 2 cyanoacrylate + methacryloxysulphone

### **Mechanism of adhesion:**

In contact with hydroxide ions (liquids like blood or water, air humidity) the cyanoacrylates form long, strong waterproof chains in an exothermic reaction. The resulting polymer leads to a stable adhesive bond. The polymerisation time is 20 sec to 2 min. with too much moisture the reaction runs too fast for a tissue adhesion.

Advantages:

- Good adhesion in moderate wet environments.
- Strong adhesion.

Disadvantages:

- Toxic degradation products.

- Heat generation during polymerization.

Gelatin resorcinol formaldehyde/glutaraldehyde glues:

These were introduced in 1966.

Mechanism of adhesion:

Resorcinol and dialdehyde react to a 3 dimensional network. Gelatine serves as filler.

Polymerisation time is 2 min, the degradation products are much less toxic as those of the cyanoacrylates.

Note: this is not used in otorhinolaryngology widely due to difficult application.

Albumin glutaraldehyde:

Mechanism of adhesion:

The glutaraldehyde molecules band together by covalent bond with the added albumin as well as with the proteins of the tissue. The polymerisation time starts immediately after mixture of the components. The entire adhesive strength is achieved after 2 min.

Note: because of its adhesion attributes in wet environments, this adhesive seems to be appropriate in otorhinolaryngology.

Role in ENT:

Role in otology:

- Myringoplasty, readaptation of the edges after traumatic rupture
- Ossiculoplasty (for both fixation of transplants (cartilage, ossicles) and

Implants (TORP, PORP)

- Fixation of implantable hearing system
- Otoplasty

Role in rhinology:

- Septoplasty (sealing of mucosa), closure of septal perforations, turbino-plasty, epistaxis.
- Fixation of transplants (cartilage, bone) and implants (stents) in repair of CSF leak and other surgeries.
- Dural plasty.

Role in laryngology:

- Closure of fistula.<sup>8</sup>
- Fixation of transplants and implants.

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